

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61L 29/00, 31/00	A1	(11) International Publication Number: WO 99/55396 (43) International Publication Date: 4 November 1999 (04.11.99)
(21) International Application Number: PCT/US99/08310 (22) International Filing Date: 15 April 1999 (15.04.99) (30) Priority Data: 60/083,135 27 April 1998 (27.04.98) US (71) Applicant: SURMODICS, INC. [US/US]; 9924 West 74th Street, Eden Prairie, MN 55344 (US). (72) Inventors: CHUDZIK, Stephen, J.; 11 Heather Place, St. Paul, MN 55102 (US). ANDERSON, Aron, B.; 4847 Birchwood Lane, Minnetonka, MN 55343 (US). CHAPPA, Ralph, A.; 16260 Suel Lane, Prior Lake, MN 55372 (US). KLOKE, Timothy, M.; 11705 Shannon Court #122, Eden Prairie, MN 55344 (US). (74) Agents: GOLDMAN, Philip, M. et al.; Fredrikson & Byron, P.A., 1100 International Centre, 900 Second Avenue South, Minneapolis, MN 55402 (US).		(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: BIOACTIVE AGENT RELEASE COATING (57) Abstract A coating composition for use in coating medical devices to improve their ability to release bioactive agents in vivo. The coating composition is particularly adapted for use with devices that undergo significant flexion and/or expansion in the course of their delivery and/or use, such as stents and catheters. The composition includes the bioactive agent in combination with a mixture of a first polymer component such as poly(butyl methacrylate) and a second polymer component such as poly(ethylene-co-vinyl acetate).		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

BIOACTIVE AGENT RELEASE COATING

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of provisional US patent application
5 filed April 27, 1998 and assigned Serial No. 60/083,135, the entire disclosure of
which is incorporated herein by reference.

TECHNICAL FIELD

In one aspect, the present invention relates to a process of treating medical
10 devices with coating compositions to provide the release of pharmaceutical agents
from the surface of the devices under physiological conditions. In another aspect, the
invention relates to the coating compositions, *per se*, and to devices coated with such
compositions.

15 BACKGROUND OF THE INVENTION

Many surgical interventions require the placement of a medical device into the
body. While necessary and beneficial for treating a variety of medical conditions, the
placement of metal or polymeric devices in the body gives rise to numerous
complications. Some of these complications include: increased risk of infection;
20 initiation of a foreign body response resulting in inflammation and fibrous
encapsulation; and initiation of a wound healing response resulting in hyperplasia and
restenosis. These, and other complications must be dealt with when introducing a
metal or polymeric device into the body.

One approach to reducing the potential harmful effects of such an introduction
25 is to attempt to provide a more biocompatible device. While there are several
methods available to improve the biocompatibility of devices, one method which has
met with limited success is to provide the device with the ability to deliver bioactive
compounds to the vicinity of the implant. By so doing, some of the harmful effects
associated with the implantation of medical devices can be diminished. Thus, for
30 example, antibiotics can be released from the surface of the device to minimize the

- 2 -

possibility of infection, and anti-proliferative drugs can be released to inhibit hyperplasia. Another benefit to the local release of bioactive agents is the avoidance of toxic concentrations of drugs which are sometimes necessary, when given systemically, to achieve therapeutic concentrations at the site where they are needed.

5 Although the potential benefits expected from the use of medical devices capable of releasing pharmaceutical agents from their surfaces is great, the development of such medical devices has been slow. This development has been hampered by the many challenges that need to be successfully overcome when undertaking said development. Some of these challenges are: 1) the requirement, in
10 some instances, for long term release of bioactive agents; 2) the need for a biocompatible, non-inflammatory device surface; 3) the need for significant durability, particularly with devices that undergo flexion and/or expansion when being implanted or used in the body; 4) concerns regarding processability, to enable the device to be manufactured in an economically viable and reproducible manner; and 5)
15 the requirement that the finished device be sterilizable using conventional methods.

 Several implantable medical devices capable of delivering medicinal agents have been described. Several patents are directed to devices utilizing biodegradable or bioresorbable polymers as drug containing and releasing coatings, including Tang
20 *et al*, U.S. patent 4,916,193 and MacGregor, U.S. patent 4,994,071. Other patents are directed to the formation of a drug containing hydrogel on the surface of an implantable medical device, these include Amiden *et al*, U.S. patent 5,221,698 and Sahatjian, U.S. patent 5,304,121. Still other patents describe methods for preparing coated intravascular stents via application of polymer solutions containing dispersed
25 therapeutic material to the stent surface followed by evaporation of the solvent. This method is described in Berg *et al*, U.S. patent 5,464,650.

 However, there remain significant problems to be overcome in order to provide a therapeutically significant amount of a bioactive compound on the surface of the implantable medical device. This is particularly true when the coating composition must be kept on the device in the course of flexion and/or expansion of
30 the device during implantation or use. It is also desirable to have a facile and easily

- 3 -

processable method of controlling the rate of bioactive release from the surface of the device.

Although a variety of hydrophobic polymers have previously been described for use as drug release coatings, Applicant has found that only a small number possess the physical characteristics that would render them useful for implantable medical devices which undergo flexion and/or expansion upon implantation. Many polymers which demonstrate good drug release characteristics, when used alone as drug delivery vehicles, provide coatings that are too brittle to be used on devices which undergo flexion and/or expansion. Other polymers can provoke an inflammatory response when implanted. These or other polymers demonstrate good drug release characteristics for one drug but very poor characteristics for another.

Some polymers show good durability and flexibility characteristics when applied to devices without drug, but lose these favorable characteristics when drug is added. Furthermore, often times the higher the concentration of drugs or the thicker the application of polymer to the device surface, the poorer the physical characteristics of the polymer become. It has been very difficult to identify a polymer which provides the proper physical characteristics in the presence of drugs and one in which the drug delivery rate can be controlled by altering the concentration of the drug in the polymer or the thickness of the polymer layer.

There remains a need, therefore, for an implantable medical device that can undergo flexion and/or expansion upon implantation, and that is also capable of delivering a therapeutically significant amount of a pharmaceutical agent or agents from the surface of the device.

BRIEF DESCRIPTION OF THE DRAWING

In the Drawing:

Figure 1 provides a plot showing the cumulative release profiles for wires coated with compositions according to the present invention, as described in Example 1.

30

- 4 -

SUMMARY OF THE INVENTION

The present invention provides a coating composition and related method for using the composition to coat an implantable medical device with a bioactive agent in a manner that permits the surface to release the bioactive agent over time when
5 implanted *in vivo*. In a particularly preferred embodiment, the device is one that undergoes flexion and/or expansion in the course of implantation or use *in vivo*.

The composition comprises a bioactive agent in combination with a plurality of polymers, including a first polymer component and a second polymer component. The polymer components are adapted to be mixed to provide a mixture that exhibits
10 an optimal combination of physical characteristics (e.g., adherence, durability, flexibility) and bioactive release characteristics as compared to the polymers when used alone or in admixture with other polymers previously known. In a preferred embodiment the composition comprises at least one poly(alkyl)(meth)acrylate, as a first polymeric component and poly(ethylene-co-vinyl acetate) ("pEVA") as a second
15 polymeric component.

The composition and method can be used to control the amount and rate of bioactive agent (e.g., drug) release from one or more surfaces of implantable medical devices. In a preferred embodiment, the method employs a mixture of hydrophobic polymers in combination with one or more bioactive agents, such as a pharmaceutical
20 agent, such that the amount and rate of release of agent(s) from the medical device can be controlled, e.g., by adjusting the relative types and/or concentrations of hydrophobic polymers in the mixture. For a given combination of polymers, for instance, this approach permits the release rate to be adjusted and controlled by simply adjusting the relative concentrations of the polymers in the coating mixture.
25 This obviates the need to control the bioactive release rate by polymer selection, multiple coats, or layering of coats, and thus greatly simplifies the manufacture of bioactive-releasing implantable medical devices.

A preferred coating of this invention includes a mixture of two or more polymers having complementary physical characteristics, and a pharmaceutical agent
30 or agents applied to the surface of an implantable medical device which undergoes

- 5 -

flexion and/or expansion upon implantation or use. The applied coating is cured (e.g., solvent evaporated) to provide a tenacious and flexible bioactive-releasing coating on the surface of the medical device. The complementary polymers are selected such that a broad range of relative polymer concentrations can be used without

5 detrimentally affecting the desirable physical characteristics of the polymers. By use of the polymer mixtures of the invention the bioactive release rate from a coated medical device can be manipulated by adjusting the relative concentrations of the polymers. Similarly, a spectrum of pharmaceutical agents can be delivered from the coating without the need to find a new polymer or layering the coating on the device.

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a coating composition and related method for coating an implantable medical device which undergoes flexion and/or expansion upon implantation. The structure and composition of the underlying device can be of

15 any suitable, and medically acceptable, design and can be made of any suitable material that is compatible with the coating itself. The surface of the medical device is provided with a coating containing one or more bioactive agents.

In order to provide a preferred coating, a composition is prepared to include a solvent, a combination of complementary polymers dissolved in the solvent, and the

20 bioactive agent or agents dispersed in the polymer/solvent mixture. The solvent is preferably one in which the polymers form a true solution. The pharmaceutical agent itself may either be soluble in the solvent or form a dispersion throughout the solvent.

The resultant composition can be applied to the device in any suitable fashion, e.g., it can be applied directly to the surface of the medical device, or alternatively, to

25 the surface of a surface-modified medical device, by dipping, spraying, or any conventional technique. The method of applying the coating composition to the device is typically governed by the geometry of the device and other process considerations. The coating is subsequently cured by evaporation of the solvent. The curing process can be performed at room temperature, elevated temperature, or with

30 the assistance of vacuum.

- 6 -

The polymer mixture for use in this invention is preferably biocompatible, e.g., such that it results in no induction of inflammation or irritation when implanted. In addition, the polymer combination must be useful under a broad spectrum of both absolute concentrations and relative concentrations of the polymers. This means that the physical characteristics of the coating, such as tenacity, durability, flexibility and expandability, will typically be adequate over a broad range of polymer concentrations. Furthermore, the ability of the coating to control the release rates of a variety of pharmaceutical agents can preferably be manipulated by varying the absolute and relative concentrations of the polymers.

10 A first polymer component of this invention provides an optimal combination of various structural/functional properties, including hydrophobicity, durability, bioactive agent release characteristics, biocompatibility, molecular weight, and availability (and cost).

Examples of suitable first polymers include poly(alkyl)(meth)acrylates, and in particular, those with alkyl chain lengths from 2 to 8 carbons, and with molecular weights from 50 kilodaltons to 900 kilodaltons. An example of a particularly preferred first polymer is poly n-butylmethacrylate. Such polymers are available commercially, e.g., from Aldrich, with molecular weights ranging from about 200,000 daltons to about 320,000 daltons, and with varying inherent viscosity, solubility, and form (e.g., as crystals or powder).

A second polymer component of this invention provides an optimal combination of similar properties, and particularly when used in admixture with the first polymer component. Examples of suitable second polymers are available commercially and include poly(ethylene-co-vinyl acetate) having vinyl acetate concentrations of between about 10% and about 50%, in the form of beads, pellets, granules, etc. (commercially available are 12%, 14%, 18%, 25%, 33%). pEVA co-polymers with lower percent vinyl acetate become increasingly insoluble in typical solvents, whereas those with higher percent vinyl acetate become decreasingly durable.

- 7 -

A particularly preferred polymer mixture for use in this invention includes mixtures of poly(butylmethacrylate) (pBMA) and poly(ethylene-co-vinyl acetate) copolymers (pEVA). This mixture of polymers has proven useful with absolute polymer concentrations (i.e., the total combined concentrations of both polymers in the coating composition), of between about 0.25 and about 70 percent (by weight). It has furthermore proven effective with individual polymer concentrations in the coating solution of between about 0.05 and about 70 weight percent. In one preferred embodiment the polymer mixture includes poly(n-butylmethacrylate) (pBMA) with a molecular weight of from 100 kilodaltons to 900 kilodaltons and a pEVA copolymer with a vinyl acetate content of from 24 to 36 weight percent. In a particularly preferred embodiment the polymer mixture includes poly(n-butylmethacrylate) with a molecular weight of from 200 kilodaltons to 400 kilodaltons and a pEVA copolymer with a vinyl acetate content of from 30 to 34 weight percent. The concentration of the bioactive agent or agents dissolved or suspended in the coating mixture can range from 0.01 to 90 percent, by weight, based on the weight of the final coating composition.

The bioactive (e.g., pharmaceutical) agents useful in the present invention include virtually any therapeutic substance which possesses desirable therapeutic characteristics for application to the implant site. These agents include: thrombin inhibitors, antithrombogenic agents, thrombolytic agents, fibrinolytic agents, vasospasm inhibitors, calcium channel blockers, vasodilators, antihypertensive agents, antimicrobial agents, antibiotics, inhibitors of surface glycoprotein receptors, antiplatelet agents, antimitotics, microtubule inhibitors, anti secretory agents, actin inhibitors, remodeling inhibitors, antisense nucleotides, anti metabolites, antiproliferatives, anticancer chemotherapeutic agents, anti-inflammatory steroid or non-steroidal anti-inflammatory agents, immunosuppressive agents, growth hormone antagonists, growth factors, dopamine agonists, radiotherapeutic agents, peptides, proteins, enzymes, extracellular matrix components, ACE inhibitors, free radical scavengers, chelators, antioxidants, anti polymerases, antiviral agents, photodynamic therapy agents, and gene therapy agents.

- 8 -

A coating composition of this invention is preferably used to coat an implantable medical device that undergoes flexion or expansion in the course of its implantation or use *in vivo*. The words "flexion" and "expansion" as used herein with regard to implantable devices will refer to a device, or portion thereof, that is bent
5 (e.g., by at least 45 degrees or more) and/or expanded (e.g., to more than twice its initial dimension), either in the course of its placement, or thereafter in the course of its use *in vivo*.

Examples of suitable catheters include urinary catheters, which would benefit from the incorporation of antimicrobial agents (e.g., antibiotics such as vancomycin or
10 norfloxacin) into a surface coating, and intravenous catheters which would benefit from antimicrobial agents and or from antithrombotic agents (e.g., heparin, hirudin, coumadin). Such catheters are typically fabricated from such materials as silicone rubber, polyurethane, latex and polyvinylchloride.

The coating composition can also be used to coat stents, e.g., either self-
15 expanding stents (such as the Wallstent variety), or balloon-expandable stents (as are available in a variety of styles, for instance, Gianturco-Roubin, Palmaz-Shatz, Wiktor, Strecker, ACS Multi-Link, Cordis, AVE Micro Stent), which are typically prepared from materials such as stainless steel or tantalum.

A coating composition of the present invention can be used to coat an implant
20 surface using any suitable means, e.g., by dipping, spraying and the like. The suitability of the coating composition for use on a particular material, and in turn, the suitability of the coated composition can be evaluated by those skilled in the art, given the present description.

The overall weight of the coating upon the surface is typically not important.
25 The weight of the coating attributable to the bioactive agent is preferably in the range of about 0.05 mg to about 10 mg of bioactive agent per cm² of the gross surface area of the device. More preferably, the weight of the coating attributable to the bioactive is between about 1 mg and about 5 mg of bioactive agent per cm² of the gross surface area of the device. This quantity of drug is generally required to provide adequate
30 activity under physiological conditions.

- 9 -

In turn, the coating thickness of a presently preferred composition will typically be in the range of about 5 micrometers to about 100 micrometers. This level of coating thickness is generally required to provide an adequate density of drug to provide adequate activity under physiological conditions.

5 The invention will be further described with reference to the following non-limiting Examples. It will be apparent to those skilled in the art that many changes can be made in the embodiments described without departing from the scope of the present invention. Thus the scope of the present invention should not be limited to the embodiments described in this application, but only by the embodiments described by
10 the language of the claims and the equivalents of those embodiments. Unless otherwise indicated, all percentages are by weight.

Examples

Test Methods

15 The potential suitability of particular coated compositions for in vivo use can be determined by a variety of methods, including the Durability, Flexibility and Release Tests, examples of each of which are described herein.

Sample Preparation

 One millimeter diameter stainless steel wires (e.g. 304 grade) are cut into 5
20 centimeter lengths. The wire segments can be Parylene treated or evaluated with no treatment. The wire segments are weighed on a micro-balance.

 Bioactive agent/polymer mixtures are prepared at a range of concentrations in an appropriate solvent, in the manner described herein. The coating mixtures are applied to respective wires, or portions thereof, by dipping or spraying, and the coated
25 wires are allowed to cure by solvent evaporation. The coated wires are re-weighed. From this weight, the mass of the coating is calculated, which in turn permits the mass of the coated polymer(s) and bioactive agent to be determined. The coating thickness can be measured using any suitable means, e.g., by the use of a microprocessor coating thickness gauge (Minitest 4100).

- 10 -

The Durability and Flexibility of the coated composition can be determined in the following manner.

Durability Test

A suitable Durability Test, involves a method in which a coated specimen
5 (e.g., wire) is subjected to repeated frictional forces intended to simulate the type of wear the sample would be exposed to in actual use, such as an implantable device undergoing flexion and/or expansion in the course of its implantation or use.

The Test described below employs a repetitive 60 cycle treatment, and is used to determine whether there is any change in force measurements between the first 5
10 cycles and the last 5 cycles, or whether there is any observable flaking or scarring detectable by scanning electron microscopy ("SEM") analysis. Regenerated cellulose membrane is hydrated and wrapped around a 200 gram stainless steel sled. The cellulose membrane is clipped tightly on the opposite side of the sled. The sled with rotatable arm is then attached to a 250 gram digital force gauge with computer
15 interface. The testing surface is mounted on a rail table with micro-stepper motor control. The wires are clamped onto the test surface. The cellulose covered sled is placed on top of the wires. Initial force measurements are taken as the sled moves at 0.5 cm/sec over a 5 cm section for 5 push/pull cycles. The sled then continues cycling over the coated samples for 50 push/pull cycles at 5 cm/sec to simulate abrasion. The
20 velocity is then reduced to 0.5 cm/sec and the final force measurements are taken over another 5 push/pull cycles.

SEM micrographs are taken of abraded and nonabraded coated wires to evaluate the effects of the abrasion on the coating.

Flexibility Test

25 A suitable Flexibility Test, in turn, can be used to detect imperfections (when examined by scanning electron microscopy) that develop in the course of flexing of a coated specimen, an in particular, signs of cracking at or near the area of a bend.

A wire specimen is obtained and coated in the manner described above. One end of the coated wire (1.0 cm) is clamped in a bench vice. The free end of the wire
30 (1.0 cm) is held with a pliers. The wire is bent until the angle it forms with itself is

- 11 -

less than 90 degrees. The wire is removed from the vice and examined by SEM to determine the effect of the bending on the coating.

Bioactive Agent Release Assay

A suitable Bioactive Agent Release Assay, as described herein, can be used to
5 determine the extent and rate of drug release under physiological conditions. In general it is desirable that less than 50% of the total quantity of the drug released, be released in the first 24 hours. It is frequently desirable for quantities of drug to be released for a duration of at least 30 days. After all the drug has been released, SEM evaluation should reveal a coherent and defect free coating.

10 Each coated wire is placed in a test tube with 5 mls of PBS. The tubes are placed on a rack in an environmental orbital shaker and agitated at 37°C. At timed intervals, the PBS is removed from the tube and replaced with fresh PBS. The drug concentration in each PBS sample is determined using the appropriate method.

After all measurable drug has been released from the coated wire, the wire is
15 washed with water, dried, re-weighed, the coating thickness re-measured, and the coating quality examined by SEM analysis.

Example 1

Release of Hexachlorophene from Coated Stainless Steel Wires

A one millimeter diameter stainless steel wire (304 grade) was cut into two
20 centimeter segments. The segments were treated with Parylene C coating composition (Parylene is a trademark of the Union Carbide Corporation). This treatment deposits a thin, conformal, polymeric coating on the wires.

Four solutions were prepared for use in coating the wires. The solutions included mixtures of: pEVA (33 weight percent vinyl acetate, from Aldrich Chemical
25 Company, Inc.); poly(butyl methacrylate "pBMA") (337,000 average molecular weight, from Aldrich Chemical Company, Inc.); and hexachlorophene ("HCP") from Sigma Chemical Co., dissolved in tetrahydrofuran. The solutions were prepared as follows:

- 1) 10 mg/ml pEVA//60mg/ml pBMA//100mg/ml HCP
- 30 2) 35 mg/ml pEVA//35mg/ml pBMA//100mg/ml HCP

- 12 -

3) 60 mg/ml pEVA//10mg/ml pBMA//100mg/ml HCP

4) 0 mg/ml pEVA//0mg/ml pBMA//100mg/ml HCP

Nine wire segments were coated with each coating solution. The following protocol was followed for coating the wire segments. The Parylene-treated wire segments were wiped with an isopropyl alcohol dampened tissue prior to coating. The wire segments were dipped into the coating solution using a 2cm/second dip speed. The wire segments were immediately withdrawn from the coating solution at a rate of 1cm/second, after which the coated segments were air-dried at room temperature.

Individual wire segments were placed in tubes containing 2 ml of phosphate buffered saline ("PBS", pH 7.4). The tubes were incubated at 37 degrees centigrade on an environmental, orbital shaker at 100 rotations/minute. The PBS was changed at 1 hour, 3 hours, and 5 hours on the first day, and daily thereafter. The PBS samples were analyzed for HCP concentration by measuring the absorbance of the samples at 298 nms on a UV/visible light spectrophotometer and comparing to an HCP standard curve.

Results are provided in Figure 1, which demonstrates the ability to control the elution rate of a pharmaceutical agent from a coated surface by varying the relative concentrations of a polymer mixture described by this invention.

Example 2

The polymers described in this disclosure have been evaluated using an Assay protocol as outlined above. The polymer mixtures evaluated have ranged from 100% pBMA to 100% pEVA. Representative results of those evaluations are summarized below.

Control coatings that are made up entirely of pBMA are very durable showing no signs of wear in the Durability Test. When subjected to the Flexibility Test, however, these coatings develop cracks, particularly in the presence of significant concentrations of drug. These coatings also release drug very slowly.

Control coatings that are made up entirely of pEVA, in contrast, are less durable and show no signs of cracking in the Flexibility Test, but develop significant

- 13 -

scarring in the Durability Test. These coatings release drugs relatively rapidly, usually releasing more than 50% of the total within 24 hours.

- Coatings of the present invention, which contain a mixture of both polymers, are very durable, with no signs of wear in the Durability Test and no cracking in the
- 5 Flexibility Test. Drug release from these coatings can be manipulated by varying the relative concentrations of the polymers. For instance, the rate of drug release can be controllably increased by increasing the relative concentration of pEVA.

- Bioactive agent containing coatings which show no signs of scarring in the Durability Test and no cracking in the Flexibility Test possess the characteristics
- 10 necessary for application to medical devices that undergo flexion and/or expansion in the course of implantation and/or use.

CLAIMS

What is claimed is:

- 5 1. A composition for coating the surface of a medical device with a bioactive agent in a manner that permits the coated surface to release the bioactive agent over time when implanted *in vivo*, the composition comprising a bioactive agent in combination with a plurality of polymers, including a first polymer component comprising at least one poly(alkyl)(meth)acrylate and a second polymer component
10 comprising poly(ethylene-co-vinyl acetate).
2. A composition according to claim 1 wherein the device is one that undergoes flexion and/or expansion in the course of implantation or use *in vivo*.
3. A composition according to claim 1 wherein the composition permits
15 the amount and rate of release of agent(s) from the medical device to be controlled by adjusting the relative types and/or concentrations of polymers in the mixture.
4. A composition according to claim 1 wherein the first polymer component is selected from the group consisting of poly(alkyl)(meth)acrylates with alkyl chain lengths from 2 to 8 carbons.
5. A composition according to claim 4 wherein the first polymer
20 component has a molecular weight of from 50 kilodaltons to 900 kilodaltons.
6. A composition according to claim 5 wherein the first polymer component comprises poly n-butylmethacrylate.
7. A composition according to claim 1 wherein the second polymer component is selected from the group consisting of poly(ethylene-co-vinyl acetate)
25 polymers having vinyl acetate concentrations of between about 10% and about 50% by weight.
8. A composition according to claim 7 wherein the vinyl acetate concentrations are between about 24% and about 36% by weight.
9. A composition according to claim 8 wherein the vinyl acetate
30 concentrations are between about 30% and about 34% by weight.

- 15 -

10. A composition according to claim 1 wherein the composition comprises a mixture of poly(n-butylmethacrylate) and poly(ethylene-co-vinyl acetate).

11. A composition according to claim 10 wherein the total combined concentrations of both polymers in the coating composition is between about 0.25% and about 70% by weight.

12. A composition according to claim 10 wherein the poly(n-butylmethacrylate) has a molecular weight of from 100 kilodaltons to 900 kilodaltons and the poly(ethylene-co-vinyl acetate) provides a vinyl acetate content of from 24% to 36% by weight.

13. A composition according to claim 12 wherein the poly(n-butylmethacrylate) has a molecular weight of from 200 kilodaltons to 400 kilodaltons and the poly(ethylene-co-vinyl acetate) provides a vinyl acetate content of from 30% to 34% by weight.

14. A composition according to claim 1 wherein the composition further comprises a solvent in which the polymers form a true solution.

15. A composition according to claim 1 wherein the bioactive agent is dissolved or suspended in the coating mixture at a concentration of 0.01% to 90% by weight.

16. A composition according to claim 15 wherein the bioactive agent is selected from the group consisting of thrombin inhibitors, antithrombogenic agents, thrombolytic agents, fibrinolytic agents, vasospasm inhibitors, calcium channel blockers, vasodilators, antihypertensive agents, antimicrobial agents, antibiotics, inhibitors of surface glycoprotein receptors, antiplatelet agents, antimitotics, microtubule inhibitors, anti secretory agents, actin inhibitors, remodeling inhibitors, antisense nucleotides, anti metabolites, antiproliferatives, anticancer chemotherapeutic agents, anti-inflammatory steroid or non-steroidal anti-inflammatory agents, immunosuppressive agents, growth hormone antagonists, growth factors, dopamine agonists, radiotherapeutic agents, peptides, proteins, enzymes, extracellular matrix components, inhibitors, free radical scavengers, chelators, antioxidants, anti polymerases, antiviral agents, photodynamic therapy agents, and gene therapy agents.

- 16 -

17. A composition according to claim 1 wherein the device is one that undergoes flexion and/or expansion in the course of implantation or use *in vivo*, the composition permits the amount and rate of release of agent(s) from the medical device to be controlled by adjusting the relative types and/or concentrations of
5 polymers in the mixture.

18. A composition according to claim 17 wherein the first polymer component is selected from the group consisting of poly(alkyl)(meth)acrylates with alkyl chain lengths from 2 to 8 carbons, and the second polymer component is selected from the group consisting of poly(ethylene-co-vinyl acetate) polymers having
10 vinyl acetate concentrations of between about 10% and about 50% by weight.

19. A composition according to claim 18 wherein the total combined concentrations of both polymers in the coating composition is between about 0.25% and about 70% by weight, and the composition further comprises a solvent in which the polymers form a true solution.

20. A composition according to claim 19 wherein the poly(n-butylmethacrylate) has a molecular weight of from 100 kilodaltons to 900 kilodaltons and the poly(ethylene-co-vinyl acetate) provides a vinyl acetate content of from 24% to 36% by weight, and the bioactive agent is dissolved or suspended in the coating mixture at a concentration of 0.01% to 90% by weight.

21. A combination comprising a medical device coated with a composition according to claim 1.

22. A combination according to claim 21 wherein the device is one that undergoes flexion and/or expansion in the course of implantation or use *in vivo*.

23. A combination according to claim 22 wherein the first polymer
25 component is selected from the group consisting of poly(alkyl)(meth)acrylates with alkyl chain lengths from 2 to 8 carbons, and the second polymer component is selected from the group consisting of poly(ethylene-co-vinyl acetate) polymers having vinyl acetate concentrations of between about 10% and about 50% by weight.

24. A combination according to claim 23 wherein the composition
30 comprises a mixture of poly(n-butylmethacrylate) and poly(ethylene-co-vinyl acetate).

- 17 -

25. A combination according to claim 24 wherein the total combined concentrations of both polymers in the coating composition is between about 0.25% and about 70% by weight, and the bioactive agent is dissolved or suspended in the coating mixture at a concentration of 0.01% to 90% by weight.

5 26. A combination according to claim 22 wherein the medical device undergoes flexion or expansion by being bent by at least 45 degrees or more and/or expanded to more than twice its initial dimension, either in the course of its placement, or thereafter in the course of its use *in vivo*.

10 27. A combination according to claim 21 wherein the device is selected from the group consisting of catheters and stents.

28. A combination according to claim 26 wherein the catheter is selected from the group consisting of urinary catheters and intravenous catheters.

15 29. A combination according to claim 21 wherein the weight of the coating attributable to the bioactive agent is in the range of about 0.05 mg to about 10 mg of bioactive agent per cm² of the gross surface area of the device.

30. A combination according to claim 29 wherein the weight of the coating attributable to the bioactive agent is between about 1 mg and about 5 mg of bioactive agent per cm² of the gross surface area of the device, and the coating thickness of the composition is in the range of about 5 micrometers to about 100 micrometers.

20 31. A method of preparing a combination according to claim 21, the method comprising the steps of providing a composition according to claim 1 and applying the composition to the medical device.

32. A method according to claim 31 wherein the coating is provided by dipping or spraying the device with the composition.

25 33. A method according to claim 32 wherein the coating composition includes a solvent and the coating upon the device is cured by evaporation of the solvent.

34. A method according to claim 31 wherein the device is one that undergoes flexion and/or expansion in the course of implantation or use *in vivo*.

- 18 -

35. A method according to claim 34 wherein the first polymer component is selected from the group consisting of poly(alkyl)(meth)acrylates with alkyl chain lengths from 2 to 8 carbons, and the second polymer component is selected from the group consisting of poly(ethylene-co-vinyl acetate) polymers having vinyl acetate
5 concentrations of between about 10% and about 50% by weight.

36. A method according to claim 35 wherein the composition comprises a mixture of poly(n-butylmethacrylate) and poly(ethylene-co-vinyl acetate).

37. A method according to claim 35 wherein the total combined concentrations of both polymers in the coating composition is between about 0.25%
10 and about 70% by weight.

38. A method according to claim 37 wherein the bioactive agent is dissolved or suspended in the coating mixture at a concentration of 0.01% to 90% by weight.

39. A method according to claim 31 wherein the weight of the coating
15 attributable to the bioactive agent is in the range of about 0.05 mg to about 10 mg of bioactive agent per cm² of the gross surface area of the device.

40. A method according to claim 39 wherein the weight of the coating attributable to the bioactive agent is between about 1 mg and about 5 mg of bioactive agent per cm² of the gross surface area of the device, and the coating thickness of the
20 composition is in the range of about 5 micrometers to about 100 micrometers.

41. A method of using a combination of claim 21, the method comprising the steps of a) implanting the device *in vivo* under conditions in which the device undergoes flexion or expansion by being bent by at least 45 degrees or more and/or expanded to more than twice its initial dimension, either in the course of its
25 placement, or thereafter in the course of its use *in vivo*, and b) permitting the device to remain implanted and to release the bioactive agent *in situ*.

42. A method according to claim 41 wherein the composition comprises a mixture of poly(n-butylmethacrylate) and poly(ethylene-co-vinyl acetate).

43. A method according to claim 41 wherein the device is selected from
30 the group consisting of catheters and stents.

- 19 -

44. A method according to claim 43 wherein the catheter is selected from the group consisting of urinary catheters and intravenous catheters.

45. A method according to claim 41 wherein the weight of the coating attributable to the bioactive agent is in the range of about 0.05 mg to about 10 mg of
5 bioactive agent per cm² of the gross surface area of the device and the coating thickness of the composition is in the range of about 5 micrometers to about 100 micrometers.

46. A system comprising a coated device combination according to claim 21 positioned *in situ* within a body.

10 47. A system according to claim 46 wherein the device is one that undergoes flexion and/or expansion in the course of implantation or use *in vivo*.

48. A system according to claim 46 wherein the composition comprises a mixture of poly(n-butylmethacrylate) and poly(ethylene-*co*-vinyl acetate).

15 49. A method according to claim 46 wherein the device is selected from the group consisting of catheters and stents.

50. A system according to claim 46 wherein the weight of the coating attributable to the bioactive agent is in the range of about 0.05 mg to about 10 mg of bioactive agent per cm² of the gross surface area of the device, and the coating thickness of the composition is in the range of about 5 micrometers to about 100
20 micrometers.

1/1

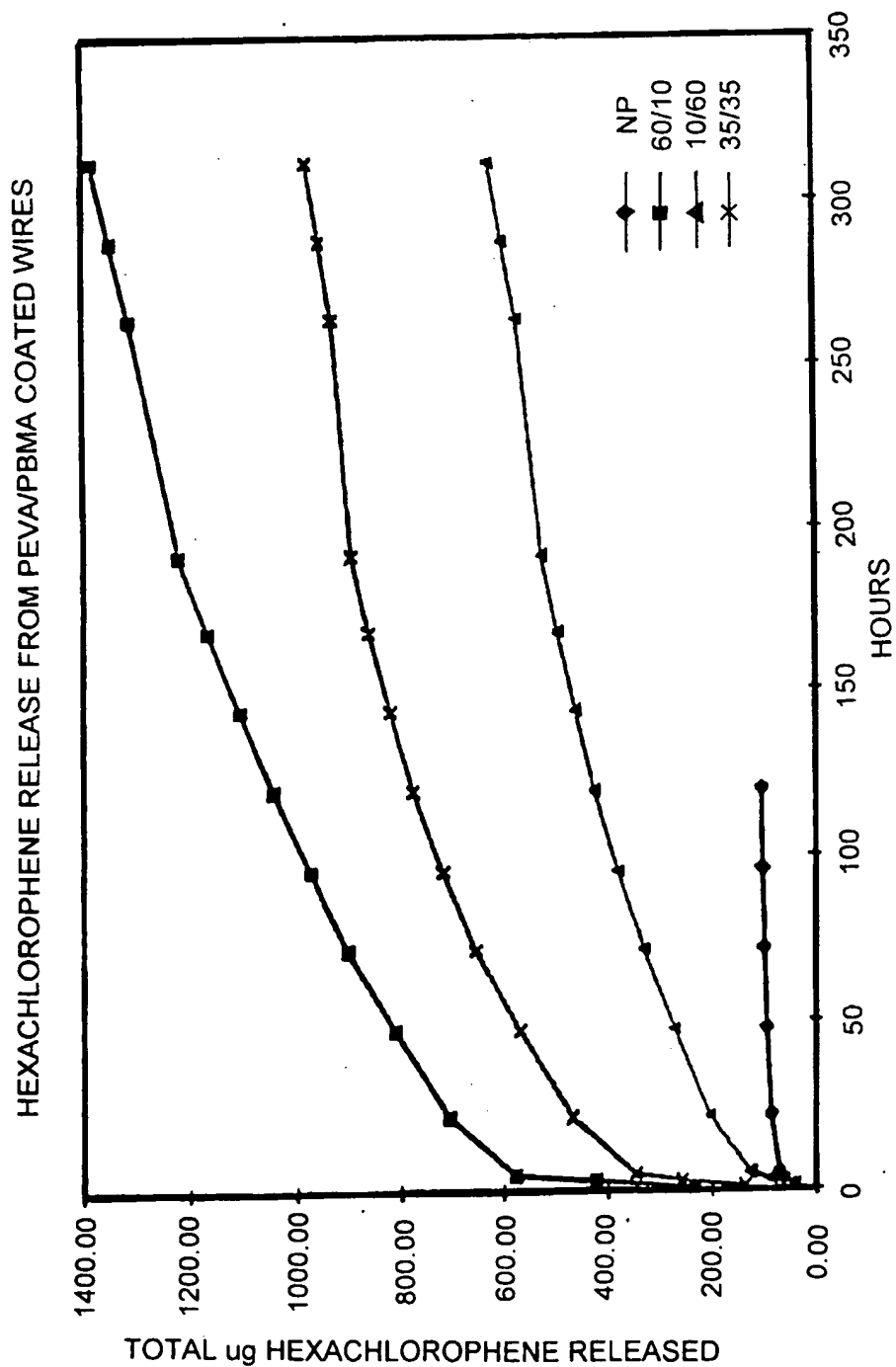


Figure 1

INTERNATIONAL SEARCH REPORT

Inte. onal Application No

PCT/US 99/08310

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L29/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 464 650 A (BERG ERIC P ET AL) 7 November 1995 (1995-11-07) cited in the application</p> <p>abstract; examples column 2, line 51-59 column 4, line 65-67 column 5, line 1-39</p> <p>---</p> <p>-/--</p>	<p>1-6,10, 14,16, 17, 21-24, 27,28, 33,34, 36, 41-44, 46-49</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

24 August 1999

Date of mailing of the international search report

31/08/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016.

Authorized officer

Böhm, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/08310

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 747 069 A (COOK INC) 11 December 1996 (1996-12-11) abstract; claim 3 column 2, line 44-54 column 13, line 56 - column 14, line 4,54 ----	1-6,10, 15-17, 21-23, 27,28, 32,34, 36,42-49
A	WO 92 11895 A (BOSTON SCIENT CORP) 23 July 1992 (1992-07-23) abstract page 2, line 29 ----	1-3,16, 21,41-44
A	US 5 578 075 A (DAYTON MICHAEL P) 26 November 1996 (1996-11-26) abstract column 1, line 15-19,23 - column 4, line 14-19 column 7, line 3,11 ----	1,4
X,P	WO 98 17331 A (COOK INC ;MED INST INC (US)) 30 April 1998 (1998-04-30) page 1, line 2-5,7-11 - page 2, line 3-5 page 3, line 26-31 - page 4, line 1-20 page 9, line 9,10,16,17 - page 20-21, line 15-31,,25-30 page 22, line 1,2 -----	1,7,21, 23,24, 31,34,35

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Appl. Application No

PCT/US 99/08310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5464650 A	07-11-1995	EP 0623354 A	09-11-1994
		JP 8033718 A	06-02-1996
		US 5837008 A	17-11-1998
		US 5679400 A	21-10-1997
		US 5624411 A	29-04-1997
		US 5776184 A	07-07-1998
		US 5824048 A	20-10-1998
EP 0747069 A	11-12-1996	US 5609629 A	11-03-1997
		AU 5588896 A	19-12-1996
		CA 2178541 A	08-12-1996
		JP 9099056 A	15-04-1997
		WO 9817331 A	30-04-1998
		US 5824049 A	20-10-1998
		US 5873904 A	23-02-1999
WO 9211895 A	23-07-1992	CA 2098984 A	29-06-1992
		EP 0565604 A	20-10-1993
		EP 0920843 A	09-06-1999
		JP 6503984 T	12-05-1994
		WO 9211896 A	23-07-1992
		US 5674192 A	07-10-1997
		US 5843089 A	01-12-1998
US 5578075 A	26-11-1996	US 5304121 A	19-04-1994
US 5578075 A	26-11-1996	US 5449382 A	12-09-1995
WO 9817331 A	30-04-1998	US 5609629 A	11-03-1997
		US 5824049 A	20-10-1998
		US 5873904 A	23-02-1999
		AU 5588896 A	19-12-1996
		CA 2178541 A	08-12-1996
		EP 0747069 A	11-12-1996
		JP 9099056 A	15-04-1999
		AU 4995997 A	15-05-1998